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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No	Applicant(s)
09/486,062	Holzemann
Examiner	**Group Art Unit**
David Lukton	1653

X Responsive to communication(s) filed on *Jan 22, 2001*

This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

X Claim(s) *1-20* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *1-20* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Pursuant to the directives of paper No. 9 (filed 1/22/01), claim 6 has been amended, and claim 20 added. Claims 1-20 are pending. The previously imposed restriction is withdrawn herewith.

Claims 1-20 are examined in this Office action.

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35 U.S.C §101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 8-10 are rejected under 35 U.S.C §101 because "use" is not a proper statutory class.

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Claims 7 and 10 are rejected under 35 USC §101 because the claimed invention is not supported by a well established utility.

Claim 7 (and claim 10) recites that the diseases in question can be "controlled". This implies that 100% of diseases can be eradicated in 100% of patients, a proposition which is difficult to prove even with extensive clinical data. It is suggested that the term treatment be used, rather than control (although the §112, first paragraph rejection will still apply).

Claims 7 and 10 are also rejected under 35 USC §112 first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

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The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification asserts (pp. 19-20) that the compounds are useful to treat circulatory disorders, thrombosis, cardiac infarction, coronary heart disease, arteriosclerosis, apoplexy, angina pectoris, cancer, osteoporosis, inflammation, infections, restenosis and rheumatoid arthritis. However, as indicated previously, none of the compounds has been shown to be useful in any assay. Applicants have argued that others are free to determine whether any of the claimed compounds have any use. However, it is applicants burden, rather than that of potential practioners, to establish that the compounds can be used in accordance with the asserted utility. Applicants have also pointed to a German patent, and a European Patent, and argued, in effect, that *In re Jolles* gives people license to assert that they do not have to comply with §112 first paragraph, if they assert that their compounds are "structurally similar" to those that have been patented by others. It is the view of the examiner that *Jolles* does not say this at all; applicants are requested to point out the specific passage in

Jolles where this is stated. In addition, this is contrary to the principle of *Brenner v. Manson*, wherein two very close homologs were at issue. In that case the structural homology (between what is claimed and the prior art) was far greater than is the case here. Moreover, even if it were true that *Jolles* effectively overturns the §112, first paragraph statute for compounds that are "structurally similar" to those that have been previously patented, the next issue would be whether indeed the compounds that are claimed are *sufficiently* related to those that have been patented so that the claimed compounds are somehow imbued with the pharmacological properties of the previously patented compounds. The examiner asserts that they are not. However, this ground of rejection will be reconsidered if applicants clearly admit on the record that the compounds now claimed are "obvious variants" of those that have been previously patented.

Next, applicants have cited *Borkowski*. Indeed, if it were true that sufficient guidance had been provided so that undue experimentation would not be required, no *in vitro* data would be required. However, *Borkowski* does not state that, where therapeutic utilities are being asserted, an applicant need not provide any data whatsoever merely because he has proposed experiments for others to carry out.

Applicants have also cited *Brana*. In that case, both *in vitro* and *in vivo* data were provided. Applicants have also argued that presumption is conferred upon their claims unless doubt can be raised. However, doubt was raised, and is raised again. As it happens, one cannot determine pharmacological activity of a given compound merely by viewing its

structure. Most randomly selected compounds are in fact devoid of activity. Even the expenditure of "undue experimentation" is no assurance that any of the compounds will have any particular activity.

In addition to the foregoing, claims 1 and 3 are rejected because of the recitation of "physiologically acceptable" salts; claim 6 is rejected because of its recitation of "pharmaceutical". These terms imply therapeutic efficacy, which is not in evidence. (A step in the direction of overcoming this rejection would be to delete the terms at issue).

The issue with respect to claim 4 is unrelated to any of the foregoing. This claim is rejected because it describes a process which is asserted to proceed for a time period which is not sufficient to obtain the stipulated result, and wherein the reaction conditions are not effective to obtain the stipulated result. This particular ground of rejection can be overcome by employing the following phrase, where appropriate: "for a time and under conditions effective to". The following format is suggested for claim 4, part (a):

A process for preparing a compound according to claim 1 comprising

(a) cyclizing a compound of formula III in the presence of a dehydrating agent for a time and under conditions effective to obtain a compound of formula I; and

(b) isolating the compound of formula I.

*

Claim 3 contains underlining or brackets that are apparently intended to appear in the

printed patent or are properly part of the claimed material. The brackets or underlining as used by the applicant are not intended to indicate amendments or changes in the claims as provided in 37 CFR 1.121(a)(2)(ii). Since underlining and brackets are normally used to indicate insertions and deletions, it is confusing to use the same in instances where the applicant desires to have the underlining and brackets appear in the published patent. If underlining or brackets are intended to appear as part of the printed patent claim, such claim should be presented in unamended form as a new claim, i.e., without the designation (amended), (twice amended), etc. as required by 37 CFR 1.121(a)(1)(B).

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Claims 1-20 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 1, line 1 recites "compounds". Here, the singular of "compounds" would be preferable, to make clear that a single compound is being claimed, rather than a mixture. Of course, if there is adequate descriptive support for it, a claim which recites a mixture could be added, such as the following:
  A mixture consisting of a compound according to claim 1, and a stereoisomer thereof.
  The same issue applies to claim 20.

- In claim 20 (and claim 1), it is recited that substituent variable "A" can be
  "-NH-NH-CO-".
  Although the resulting structure is chemically possible, it may be an error. For the case of "A" representing "-NH-NH-CO-", there will be three nitrogen atoms in a row. Such a molecule is probably not stable. Reaffirmation or correction is required.

- In claim 20 (and claim 1), it is recited that substituent variable "A" can be glycine or

alanine, "where the amino acids mentioned can also be derivatized". The following would be better, although still indefinite with regard to the derivatives that might be intended:

A is glycine or alanine, or A is a derivative of glycine or alanine; or A, taken together with the imino group to which it is bonded represents -NH-NH-CO-.

- In claim 20 (and claim 1), variables R^1 and R^2 are defined. They are being described as being "also" the indicated groups (containing R^7/R^8 or R^9/R^{10}). The use of "also" tends to suggest that variables R^1 and R^2 must be several different substituents simultaneously. It would be better to convey that there is a choice. This can be achieved by deleting "also", and using "or" where appropriate.

- In claim 20 (and claim 1), variables R^7, R^8, R^9 and R^{10} are defined. The definition of these variables should be preceded by "wherein".

- In claim 20 (and claim 1), the second-to-last line recites the following:
"and if there are radicals of optically active amino acids and amino acid derivatives"
The wording of this tends to suggest that there are "amino acid derivatives" which are not also amino acid derivatives. If the derivitization is confined to the side chain of an *alpha*-amino acid, the result will still be an amino acid. The wording of the phrase at issue could be interpreted to mean that either the carbonyl group, or the imino group (found in all amino acids) is no longer present. If this is the case, applicants are requested to provide one such example of what is intended. Otherwise, the phrase "and amino acid derivatives" can be deleted. Alternatively, if there is adequate descriptive support (and there probably isn't), the claim could simply make reference to chiral centers that might be present, and use the "R" and "S" terminology.

  The following is suggested for the last two lines:
  ...wherein the alpha-carbon of each amino acid other than glycine is either D or L; or a salt thereof.

  As indicated above, the following claim could be added, if deemed appropriate:

  A mixture consisting of a compound according to claim 1, and a stereoisomer thereof.

- The first word of claim 4, line 1 is "process". This should be preceded by the indefinite article ("a"). The same applies to claim 5.

- Line 2 of claim 4 recites a method of preparing salts of the compounds. However, process "(a)" does not explain how to do this.

- The clarity of claim 4 would be enhanced by creating two separate claims, one for process (a), and one for process (b). Preferably they will be independent, although this is not necessarily critical.

- Claim 4 is indefinite as to the process steps. Specifically, the claim fails to recite an isolation step for the final product. The following format is suggested, at least for process "(a)":

  A process for preparing a compound according to claim 1 comprising
  (a) cyclizing a compound of formula III in the presence of a dehydrating agent for a time and under conditions effective to obtain a compound of formula I; and
  (b) isolating the compound of formula I.

- Process (b) is unclear as to what is intended by "setting free" the compound of formula I from "one of its functional derivatives". Perhaps what is intended is that any protecting groups which may have been present are removed. Perhaps also applicants intend for the deprotecting step to be used following the cyclization; this would make sense from the standpoint of commonly used synthetic procedures. As the claim stands, however, it suggests that the cyclization of step (a) is done without protecting groups (which is possible, depending on what the substituent variables are) and that process (b) is done without a cyclization. While in principle there are ways of assembling the target compounds that are different from that described in part (a) of claim 4, it is difficult to see how to prepare the compounds of claim 1 without a cyclization step. Clarification is sought.

- Claim 8 is indefinite with regard to the intended pathologies. One of the issues here is, how far "upstream" or "downstream" can one go in deciding whether the process is "supported or propagated" by angiogenesis.

- Claim 8 is indefinite as to the intended illnesses.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is (703) 308-3213.

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800